Photooxygenation of N^{21},N^{22}-Bridged Isophlorin to 19-Benzoylisobilirubin

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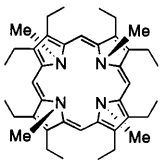
Antiaromatic isophlorin with N^{21},N^{22}-(1,2-diphenyletheno) and N^{23},N^{24}-(carboethoxymethano) double bridge was dioxygenated at the C_{meso}–$C_{pyrrole\text{-}\alpha}$ double bond of the dipyrrylmethene moiety having the N^{21},N^{22}-(1,2-diphenyletheno)-bridge, leading to an isobilirubin derivative that was characterized by X-ray crystallography.

Isophlorin as well as its isomers (phlorin, chlorin, and porphodimethenes) is a two-electron reduced form of porphyrin, and its 20π-electron cycloconjugation is quite unusual in porphyrin chemistry. In 1991, Vogel's group reported N^{21},N^{22},N^{23},N^{24}-tetramethyl-2,3,7,8,12,13,17,18-octaethylisophlorin (**1**).[1] Although this compound was the first example of isophlorin, a paramagnetic NMR ring current effect diagnostic of antiaromaticity was not observed owing to its highly saddle-shaped structure of the porphyrin nucleus (**1**-core) revealed by X-ray crystallography. We have recently obtained antiaromatic isophlorins by introduction of the N^{21},N^{22}-bridge that holds planar ring structure.[2] Isophlorin as one of the antiaromatic compounds is quite reactive and it is of interest to elucidate the reaction behavior. We describe here our finding that the photo-induced dioxygenation of N^{21},N^{22}-(1,2-diphenyletheno)-N^{23},N^{24}-(carboethoxymethano)-5,10,15,20-*meso*-tetraphenylisophlorin (**2**) occurs readily to give 19-benzoylisobilirubin **3**.



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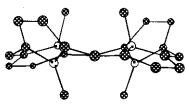
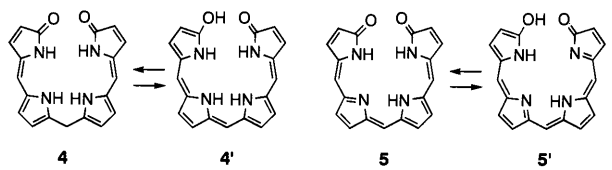


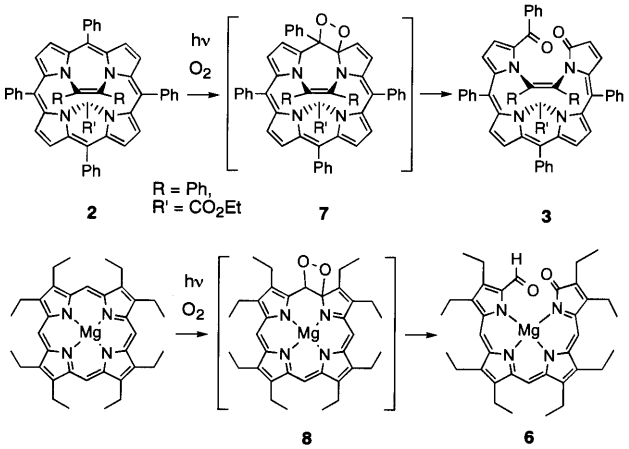
1-core

When a benzene solution of **2** (5.2×10^{-3} mol dm^{-3}) was stirred under O_2 atmosphere at room temperature for 5 h, a dark compound **3** was obtained in 73% yield after chromatographic purification on silica gel. The compound **3** shows a broad UV–vis absorption at 555 nm and the ^{1}H NMR spectrum indicates disappearance of both ring current effect and C_s molecular symmetry that are present in **2**.[3] The cleavage of the C_{meso}–$C_{pyrrole\text{-}\alpha}$ double bond in the dipyrrylmethene moiety having the N^{21},N^{22}-(1,2-diphenyletheno)-bridge was verified by X-ray crystallography as shown in Figure 1.[4] The compound **3** is 19-benzoylisobilirubin, in which the π-electron system is isoelectronic with that of the enol form **4'** of bilirubin and the hydroxyl group of **4'** is replaced by the benzoyl group.



4 **4'** **5** **5'**

Bilirubin and biliverdin usually described as 1,19-diketo forms, **4** and **5**, respectively, are biochemical degradation products of heme and their molecular chirality is drawing great attention.[5] They are formed by extrusion of one *meso*-carbon of the porphyrin core as carbon monoxide by the action of hemeoxygenase.[6] A mechanistically simpler oxidative ring opening of porphyrin was reported to give a similar linear tetrapyrrole derivative, 19-formylbiliverdin **6**, that is isoelectronic with the enol form **5'** of biliverdin.[7] This reaction is a photo-induced dioxygenation of a C_{meso}–$C_{pyrrole\text{-}\alpha}$ double bond of Mg(OEP)[8] probably via a dioxetane intermediate **8** (see Scheme 1). It is deduced that singlet oxygen formed on quenching the triplet state of Mg(OEP) reacts with the ground state of Mg(OEP). The low oxidation potential (+0.43 V vs SCE)[9] of Mg(OEP) is crucial for this novel reaction to occur. Since reduced porphyrins have lower oxidation potentials than porphyrins, chlorin and bacteriochlorin are more reactive toward singlet oxygen.[10] In this sense, the reactivity of phlorin and isophlorin is of interest.[11] Since the yield of **3** decreased to 8% in the dark under otherwise the same reaction conditions, the present reaction is remarkably promoted by room light. Thus, a similar reaction mechanism involving singlet oxygen and a dioxetane intermediate **7** is suggested in this case. The highly reactive nature of **2** is due to the remarkably low oxidation potential (–0.17 V vs Ag/AgCl in MeCN).[2]



Scheme 1.

Geometry optimization on the AM1 level of the model isophlorin, N^{21},N^{22}–(MeC=CMe)–N^{23},N^{24}–(CHMe)(isophlorin) **2'**, indicates that the dipyrrylmethene unit having the *N*,*N'*-methylene bridge is mostly planar whereas the *N*,*N'*-vinylene-bridged dipyrrylmethene is highly distorted from planarity

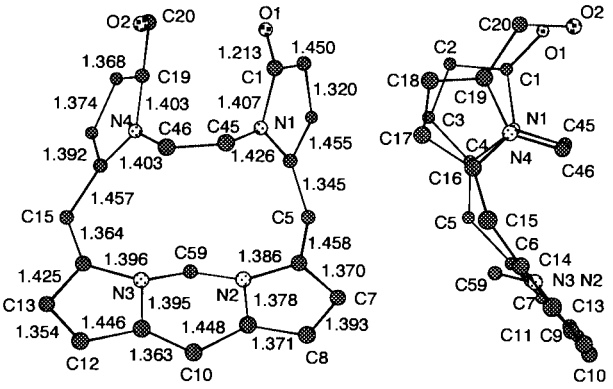


Figure 1. X-ray structure of **3**: a front view (left) and a side view (right) with atom-numbering scheme and bond lengths (Å), e.s.d. of which range from 0.004 to 0.005 Å. Six phenyl groups (at C5, C10, C15, C20, C45, and C46) and the CO_2Et group at C59 were omitted for clarity.

(Figure 2). This calculation is in agreement with the reported X-ray structures of *N,N'*-bridged porphyrins,[12] and explains the observed regioselectivity in the oxygenation reaction.[13] The X-ray structure of isobilirubin **3** shows a twisted π-electron system. That is, the dihedral angles between the mean planes of the N1-pyrrole and N2-pyrrole, of the N2-pyrrole and N3-pyrrole, and of the N3-pyrrole and N4-pyrrole are 69.1 (0.1), 4.0 (0.3), and 58.0 (0.1) degrees, respectively. It is remarkable that the face-to-face orientation of the N1-pyrrole and N4-pyrrole makes steric repulsion between the C(1)=O(1) group and the benzoyl group at C(19). Since C(20) and O(2) are very close to O(1) with distances of 2.694 and 2.904 Å, respectively, the benzoyl group is pushed away by 26.2° from the mean plane of the N4-pyrrole. The $C_{pyrrole\text{-}\alpha}$–$C_{pyrrole\text{-}\beta}$ bond length and the $C_{pyrrole\text{-}\beta}$–$C_{pyrrole\text{-}\beta}$ bond length differ by 0.07–0.13 Å in the N1- and N3-pyrroles while those are within 0.03 Å differences for the N2- and N4-pyrroles. This means that the N2- and N4-pyrroles retain well-delocalized 6π-aromatic character while the N1- and N3-pyrroles take a quinone-type electronic structure. This geometrical feature is similar to that of **1** and indicates that the π-electron conjugation between pyrroles is very weak.

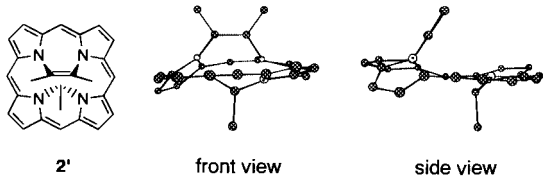


Figure 2. Calculated structure of a model isophlorin **2'**.

In conclusion, steric constraint imposed by the *N,N'*-vinylene bridge and the low oxidation potential of the isophlorin **2** cause easy photodioxygenation reaction of the C_{meso}–$C_{pyrrole\text{-}\alpha}$ double bond to give a novel isobilirubin.

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References and Notes

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3 **3**: Yield 73%; ^{1}H NMR (δ, $CDCl_3$): 7.05, 7.00, 6.49, 6.40, 6.39, 5.94, 5.64, 5.47 (d × 8, 1H × 8, pyrrole-β-H); 8.19, 7.52, 7.30, 7.14, 7.03, 6.80 (d × 6, 2H × 6, phenyl-*o*-H); 7.45, 7.41, 7.35, 7.14, 6.98, 6.92 (d × 6, 2H × 6, phenyl-*m*-H); 7.54, 7.38, 7.33, 7.16, 7.00, 6.90 (t × 6, 1H × 6, phenyl-*p*-H); 6.48 (s, 1H, CH-CO_2); 3.68, 3.58 (dq × 2, 1H × 2, J = 10.8 and 7.2 Hz, O-CH_2); 0.89 (t, 3H, CH_3); UV/vis (CH_2Cl_2): λ_{max}(log ε) 555 nm (4.15); Anal. Calcd for $C_{62}H_{44}N_4O_4{\cdot}2H_2O$: C, 78.80; H, 5.12; N, 5.93%. Found: C, 79.26; H, 5.03; N, 5.80%.

4 Crystal data for **3**: $C_{62}H_{44}N_4O_4{\cdot}(2H_2O)$, M_r = 941.05, triclinic, space group $P\bar{1}$ (#2), a = 11.7573(14), b = 12.7714(15), c = 17.771(2) Å, α = 102.128(2), β = 108.358(2), γ = 93.317(2)°, V = 2453.9(5) Å^3, Z = 2, D_{calc} = 1.274 g/cm^3, μ(Mo Kα) = 0.081 mm^{-1}, T = 299 K, crystal size 0.3 0.2 0.2 mm. A total of 9415 unique reflections out of 13487 ($2.5 < 2\theta < 54.3°$) were collected. R_1 = 0.073, wR_2 = 0.183 for 4690 reflections with $I > 2\sigma(I)$; R_1 = 0.147, wR_2 = 0.228 for all data. GOF on F^2 = 0.942.

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8 Abbreviation: OEP = octaethylporphyrin.

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13 The AM1 level calculation on model dioxetanes derived from **2'** shows that the dioxetane at the *N,N'*-vinylene-bridged dipyrrylmethene is by 4.8 Kcal/mol more stable than that at the *N,N'*-methylene-bridged dipyrrylmethene.